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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,785	03/19/2004	Frits Goedegebuur	GC793-3	7768

7590 03/09/2007

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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,785	GOEDEGEBUUR ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6 and 7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6 and 7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

Please note that the instant application/case has been transferred to examiner Ganapathirama Raghu, Art Unit 1652, whose telephone number is (571)-272-4533 and all further enquiries regarding this application should be directed to said examiner.

Claims 1-25 are pending. Claims 1-5 and 8-25 remain withdrawn.

In response to the Office Action mailed on 06/15/2006, applicants' filed a response and amendment received on 12/12/ 2006. Said amendment, amended claims 6-7. Thus, amended claims 6-7 are pending in the instant Office Action.

Objections and rejections not reiterated from the previous action are hereby withdrawn.

Priority

Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e) of US provisional applications serial number 60/456,368 filed on 03/21/2003 and 60/458,696 filed on 03/27/2003.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/10/2006, is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner is considering the IDS statement.

Withdrawn- Claim Rejections: 35 USC § 112

In view of Applicant's amendment, the previous rejection of claim 6 under 35 U.S.C. 112, second paragraph is withdrawn.

Maintained-Claim Rejections: 35 USC § 112
Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants have aligned the sequences of 5 CBHI homologs (Figure 2) and have concluded in paragraph 222 the these are "[p]ossible sites involving stability" (emphasis added) and in paragraph 223 that "sites where the residue in *H. jecorina* or *H. orientalis* is the same as that found in all of the decreased stability enzyme homologs resulted in the identification of sites that lacked correlation with Tm". In paragraph 224 they conclude that "Q186, S195, E325 and P412" "showed the best correlation with Tm stability". They then present claim 6 that is drawn to "a substitution or deletion at a position corresponding to one or more residues...T66...of the mature *H. jecorina* CBHI protein" and claim 7 that is drawn to further substitutions. Apparently none of the sequences in Figure 2 show just one of the changes in claim 6 in combination with any or all of the changes in claim 7 and none of the sequences in the figure show a deletion of one of the residues in claim 6. It is well known that the effects of different changes in an amino acid sequence cannot be predicted with any certainty and therefore applicant must show that any and all of the changes in the instant claims will produce a protein with activity. This has not been done and therefore it is maintained that undue experimentation would be required to produce active proteins with the claimed changes.

In response to the above rejection, applicants' have traversed on the basis that: "applicants' have identified possible sites involved in the stability of the CBH1 enzyme in three different ways based on alignment of the sequences of homologs of CBH1 enzyme".

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The claims as written when given the broadest interpretation reads on any variant CBH 1 cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion at a position corresponding to T66 of *H. jecorina* CBH1 protein of SEQ ID NO: 1.

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a variant *H. jecorina* CBH1, wherein in said variant the amino acid residue T66 has been deleted from the wild-type sequence of SEQ ID NO: 1. However, the specification does not reasonably provide enablement for any variant CBH 1 cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A). Furthermore, the claim language as written allows substitution at all positions of said mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claim (mere recitation of sequences from prior art in the specification does not overcome the deficiency in the scope of the claims).

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6-7 are so broad as to encompass any variant CBH 1 cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A). Furthermore, the claim language as written allows substitution at all positions of said mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of variants from any source with CBH 1 cellulase activity as broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to a variant *H. jecorina* CBH1, wherein in said variant the amino acid residue T66 has

been deleted from the wild-type sequence of SEQ ID NO: 1, but provides no guidance with regard to making and using variants of CBH1 cellulase from any source. In view of the great breadth of the claims, the amount of experimentation required to determine a use for the full scope of the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompasses any variant CBH 1 cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A), because the specification does not establish: **(A)** the desired CBH 1 activity of all polypeptides including variants from any

source; **(B)** regions of the protein/polynucleotide structure which may be modified without affecting the activity of encoded polypeptide; **(C)** the general tolerance of the polypeptide and the polynucleotide encoding to modification and extent of such tolerance; **(D)** a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function; and **(E)** the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants' have not provided sufficient guidance to enable one of ordinary skill in the art to use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a method of producing any eukaryotic glycosyltransferase including variants, mutants and recombinants from any source in a prokaryotic microorganism under specific conditions, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Written description

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As outlined supra, applicant has apparently not made and analyzed all of the mutant

CBHI enzymes of the instant claims and therefore it is maintained that at the time of filed one of skill in the art would not conclude that applicant had possession of the claimed invention.

In response to the above rejection, applicants have traversed on the basis that: "specification teaches the variant CBH 1 polypeptides comprise a substitution or deletion at apposition corresponding to one or more residues including *inter alia*, sites presently claimed in claim (T66) and claim 7 (Q186, S195, E239, G242, P412)".

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons.

Claims 6-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-7 (as interpreted), are directed to (1) a genus of variant CBH 1 polypeptides from any variant CBH 1 cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A), which have any % sequence identity to the polypeptide of SEQ ID NO:1. Furthermore, the claim language as written allows substitution at all positions of said mature *H. jecorina* CBH1 protein of SEQ ID NO: 1. While the specification discloses the structure of a variant *H. jecorina* CBH1, wherein in said variant the amino acid residue T66 has been deleted from the wild-type sequence

of SEQ ID NO: 1, the specification is silent in regard to (1) the structures and functions of all the polypeptides encompassed by the claims, (2) the critical structural elements of any variant CBH 1 polypeptide from any source wherein said variant comprises any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A), which have any % sequence identity to the polypeptide of SEQ ID NO:1.

The genus of polypeptides required in the claimed invention is an extremely large functionally and structurally variable genus. While the argument can be made that the recited genus of polypeptides is adequately described by the disclosure of the structure of the polypeptide of SEQ ID NO:1, since one could use structural homology to isolate those polypeptides recited in the claims, as taught by the art, even highly structurally homologous polypeptides do not necessarily share the same function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8): 2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Therefore, the claimed genera of polypeptides have the potentiality of encoding proteins of many different functions.

In addition, while a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, the interpreted structural feature, i.e. " variant CBH 1 polypeptides from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion, corresponding to position T66 of mature *H. jecorina* CBH1 protein of SEQ ID NO: 1 and further comprising a substitution at a position corresponding to residue Q186(E), S195(A/F), E239S, G242(H/Y/N/S/T/D/A) and P412(T/S/A), which have any % sequence identity to the polypeptide of SEQ ID NO:1", does not constitute a substantial portion of the genus as the remainder of any polypeptide comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Many functionally and structurally unrelated polypeptides are encompassed by these claims. The specification only discloses a single species of the recited genus, which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the required genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Maintained-Claim Rejections: 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by either of (A), yon der Osten, et al. (B), Schulein, et al. (C), Miettinen-Oinonen, et al. or (D) Lund. yon der Osten (A), as shown by the sequence search (V), has T66 substituted with S in SEQ ID NO:1. Schulein, et al. (B), as shown by the sequence search (W), has T66 substituted with S and T66 deleted in SEQ ID NO: 11. Meittinen-Oinonen, et al. (C), as shown by the sequence search (X), has T66 substituted in SEQ ID N0: 33 and 35. Lund, et al. (D), as shown by the sequence search (U-l), has T66 substituted by S in SEQ ID NO: 1-3.

Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Radford, et al. (A). Radford, et al., as shown by the sequence searches (U), has T66 deleted in SEQ ID NO:3, T66 substituted with S and G242 substituted with S in SEQ ID NO:2 and T66 substituted with S and G242 substituted with S in SEQ ID NO:3.

In response to the above rejection, applicants' have traversed on the basis that: "cited reference sequences have low homology to CBH 1 and are not variant CBH 1 cellulases".

Applicants' arguments have been fully considered but are not deemed persuasive for the following reasons. The claims as written when given the broadest interpretation include any cellulase from any source, wherein said variant comprises any substitution (any other 19 amino acids) or deletion at a position corresponding to T66 of *H. jecorina* CBH1 protein of SEQ ID

NO: 1. Any cellulase which differs from CBH 1 can be considered a variant CBH 1 cellulase as applicants' have not defined any limitations which must be present I such variant CBH 1 cellulase. Furthermore, the cited references have annotated their respective polypeptides as cellulases, therefore claims as written read on cited prior art references.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

1. Claims 6 and 7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement and written description.

2. Claim 6 is rejected under 35 U.S.C. 102(b) as being anticipated by either of (A), yon der Osten, et al. (B), Schulein, et al. (C), Miettinen-Oinonen, et al. or (D) Lund.

3. Claims 6-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Radford, et al.,.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Feb. 24, 2007.

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